REMARKS

Claims 1-6, 8-14, 17-19, 48, 50, 58-61 are pending in the instant application. Claim 1 has been amended to delete an unnecessary limitation that had been previously included solely for the purpose of clarifying the invention. Support for the amendment can be found at page 14, lines 2-11, and therefore, no new matter has been added by this amendment.

Claim 48 has been amended to clarify that the preparation of a hybridoma requires a step of harvesting of the immune cells from the device. Support for the amendment can be found at page 17, lines 18-23. Thus, no new matter has been added by this amendment which is fully supported by the specification and claims as originally filed.

Claim 60 has been newly added to recite a device with perforations of approximately 1/16 and 1/32 of an inch in diameter. Support for the amendment can be found at pages 21, line 19 to 22, line 4. No new matter has been added by this amendment.

Claim 61 has been newly added to recite a device with about 10 perforations per centimeter of tubing. Support for the amendment can be found at page 22, lines 18-20. Thus, no new matter has been added by this amendment.

1. REJECTION FOR DOUBLE PATENTING

Applicants thank the Examiner for acknowledging their request to hold the double patenting rejections in abeyance until allowable subject matter is identified.

2. REJECTION FOR OBVIOUSNESS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1-6, 8-14, 17-19, 48, 50, 58-61 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,593,697 by Barr et al. ("Barr") in view of U.S. Patent No. 5,529,777 by Andrianov et al. ("Andrianov"). In particular, the Examiner

asserts that Barr discloses a pharmaceutical implant with a water insoluble coat made of polymeric material that is functionally equivalent to the device of the present invention. The Examiner further argues that the present invention is obvious over Barr in view of Andrianov, because Andrianov teaches encapsulating hybridoma cells in the microspheres. The Applicants respectfully disagree, for the reasons discussed below.

2.1 The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. 2143.

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art.

Both the suggestion and the reasonable expectation of success must be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). With regard to the final point, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue.* 127 S.Ct. at 1742, 82 USPQ at 1397.

2.2 The Invention

The present invention relates to a novel implantable device containing an antigen that is designed to attract cells of the immune system to the antigen in a controlled fashion. Upon implantation, the novel implantable device has a container composed of a perforated but otherwise impermeable material and a porous matrix within that contains an antigen. The perforations in the container component of the device create a diffusion barrier that maintains optimal levels of antigen, immune cell secretory products and immune cells within the device. Page 14, lines 2-7. These perforations are designed to restrict the passive diffusion of small molecules, such as antigens, but permit the active movement of immune and other cells into and out of the device. Page 19, lines 14-18. The diffusion barrier is maintained due to the size and number of perforations in otherwise impermeable container. Page 22, line 20 to page 23, line 4.

2.3 The Claimed Invention Is Non-Obvious

Barr discloses a pharmaceutical implant with a water insoluble coat made of polymeric material equivalent to the material of the device of the present invention. Therefore, the Examiner contends that Barr device must be functionally equivalent to the present invention – *i.e.*, that the Barr device will attract cells of immune system to encounter the antigen within the device and modulate the immune response — because a composition and its properties are inseparable.

The Applicants disagree with the Examiner's contention. The Barr device lacks an essential element of the claimed invention, *i.e.*, the perforations in the outer layer of the

device of the present invention at the time of implantation. The outer layer of the claimed invention, called the "container," contains perforations in otherwise impermeable material. See page 14, line 2-7. The outer layer of the Barr device, called "film coating," does not feature any perforations at the time of implantation and, as a result, is completely impermeable prior to rupture. See Col. 5, lines 1-5. Due to this distinction, the device of the present invention operates completely differently from the Barr device.

The Examiner argues that a diffusion barrier is actually present in the Barr device because the Barr device and the present invention are composed of the same materials. The Examiner relies on *In re Spada*, 911 F.2d 705, 709 (Fed. Cir. 1990) for the principle that "products of identical chemical compositions cannot have mutually exclusive properties," leading the Examiner to conclude that immune cells must come into contact with antigen within the Barr device prior to rupture of the outer film coating. However, contrary to the Examiner's assertion, due to the absence of perforations at the time of implantation, the film coating of the Barr device fails to serve as a diffusion barrier. Immune cells will not be able to enter through the impermeable film coating of the Barr device because it lacks perforations which would otherwise permit entry of immune cells. Therefore, the Barr device will not allow immune cells to come into contact with antigen prior to rupture of the outer film coating.

Indeed, it is the structural differences between the device of the invention and the Barr device -- the presence of perforations in the device of the present invention at the time of implantation and their absence in the Barr device– that distinguish the two devices, giving the instant invention its unique property of enhancing the immune response to an antigen by providing an environment similar to a lymph node where immune cells can concentrate within the device and encounter high levels of antigen and immune factors, such as cytokines, to provide a robust immune response.

Thus, the claimed invention is not obvious in light of Barr. Furthermore, Barr provides no motivation to one of ordinary skill in the art to modify the Barr device in accordance with the device of the claimed invention. Not only does Barr fail to suggest or

provide motivation to incorporate perforations into the film, but such perforations would be contrary to the goals of Barr. The goal of Barr's invention is to provide a delayed pulsed release of antigen. Col. 3, lines 11-15. The bilayer film coating of the Barr reference forms an impermeable barrier to antigen until the failure of the inner film coating layer leads to rupture of the outer film coating layer. Col. 5, lines 2-14. Presence of perforations would frustrate the purpose of Barr's invention by facilitating the flow of physiological fluid inside Barr's device resulting in a premature rupture of the outer film layer and immediate release, rather than delayed release, of antigen.

Moreover, the method of the present invention is not obvious over Barr in view of Andrianov. Andrianov teaches the use of antigens mixed with a polymer solution for the controlled release of antigen at the target surface. Col. 4, line 66 to Col. 5, line 2; Col. 5, lines 23-31. Andrianov neither suggests an impermeable outer coating layer nor perforations in the polymer microspheres. Indeed, such perforations would serve no purpose in the delayed controlled release formulation taught by Andrianov.

Thus, the references cited by the Examiner do not suggest or provide motivation for the presently claimed invention, let alone to do so with an expectation of success. The devices of Barr and Andrianov induce an immune response in a manner different than the device of the present invention. Both the devices of Barr and Andrianov serve as delayed release formulations, and perforations in the polymer material at the time of their implantation would either frustrate the purpose of such devices or serve no purpose at all. In contrast, the novel device of the present invention is designed to enable contact between immune cells and antigen within the device, and perforations in the container component of the device enable such contact. Given the difference in purpose served by the devices of Barr and Andrianov and the device of the present invention, the introduction of perforations would not have been obvious to one of ordinary skill in the art at the time the invention was made.

In addition, newly added claims 60 and 61 recite additional limitations relating to the structural features of the perforations, specifically their size and number, in the container component of the device. These additional limitations are not disclosed in either

Barr or Andrianov, nor are they obvious over either reference or the combination of references.

The Examiner acknowledges that Barr does not teach the use of the device for generating hybridomas. However, the Examiner relies upon Andrianov to argue that it would have been obvious to one of ordinary skill in the art to use the current invention to make hybridomas. However, Andrianov fails to teach or suggest a method of preparation of a hybridoma for the production of monoclonal antibodies against a specific antigen. The Examiner points out that Andrianov discloses encapsulating hybridoma cells in the microspheres. Example 1. Contrary to the Andrianov reference, the method of present invention does not include encapsulating of hybridoma cells in the miscrospheres or in the device of the present invention. Instead, the present invention includes immunizing a mammal with an antigen contained within the device, followed by harvesting of the immune cells from the device for the subsequent production of antigen-specific hybridomas. Page 17, lines 18-23. Importantly, encapsulating of hybridoma cells in the microspheres or in the device would not achieve the purpose of the present invention, which is to generate a hybridoma for the production of monoclonal antibodies against a specific antigen. Therefore, the combination of Barr and Andrianov references will not render the current invention obvious.

Therefore, the prior art references, Barr and Andrianov, alone or taken together, neither teach nor suggest all the claim limitations of the present invention. Nor was there knowledge generally available to one of ordinary skill in the art at the time the invention was made, to modify Barr and Andrianov to include perforations in the outer layer of the device at the time of its implantation, and to carry out the modification with a reasonable expectation of success. Thus, the current invention would not have been obvious to one of ordinary skill in the art.

In view of the remarks above, the Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a). In the alternative, the Applicants respectfully request

that the Examiner support the conclusion of obviousness based on knowledge within the level of ordinary skill in the art by an affidavit pursuant to rule 37 CFR 1.104(d)(2).

CONCLUSION

Entry of the foregoing remarks and amendment into the record of the above-identified application is respectfully requested. Applicants estimate that the remarks and amendment made herein now place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Frederick J. Hamble — 42,623 (Reg. No.)

712 Kitchawan Road
Ossining, NY 10562
(914) 762-7586